REMARKS

Applicants have canceled non-elected claims 14, 15 and 30-34 without prejudice or disclaimer of the subject matter recited therein, and reserve all rights to such subject matter. Without acquiescing in any rejection, applicants have amended claims 1-4, 7, 17, 18, 22 and 25-27 in order to better claim the invention, which moots many of the indefiniteness rejections. Upon entry of this amendment, claims 1-13 and 16-29 are pending.

The claims are not taught or suggested by the prior art

On pages 3-6 of the office action, the examiner rejected claims 1-13 and 16-29 as obvious over the Kucherlapati patent in view of Mendez and Popov. Kucherlapati was cited for disclosing transgenic mice comprising germline segments of IgG loci, which can be reproduced by using murine embryonic stem cells modified to include YACs. Mendez was cited for disclosing transgenic mice having disrupted endogenous Ig heavy and light chain loci. Popov was cited for allegedly teaching the YAC disclosed in the present application. The alleged motivation and reasonable expectation of success supporting the combination of these references is set forth briefly on page 6 of the office action.

At the outset, applicants note that the examiner must show all of the recited claim elements in the combination of references that make up the rejection. When combining references to make out a *prima facie* case of obviousness, the examiner is obliged to show by citation to specific evidence in the cited references that (i) there was a suggestion/motivation to make the combination and (ii) there was a reasonable

expectation that the combination would succeed. Both the suggestion/motivation and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir. 1983) (holding that is improper in combining references to hold against the inventor what is taught in the inventor's application); *see also* MPEP §§ 2142-43 (August 2001). Thus, the examiner must provide evidentiary support based upon the contents of the prior art to support all facets of the rejection, rather than just setting forth conclusory statements, subjective beliefs or unknown authority. *See In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002).

When an examiner alleges a *prima facie* case of obviousness, such an allegation can be overcome by showing that (i) there are elements not contained in the references or within the general skill in the art, (ii) the combination is improper (for example, there is a teaching away or no reasonable expectation of success) and/or (iii) objective indicia of patentability exist (for example, unexpected results). *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 419-20 (Fed. Cir. 1986). The references are discussed with these legal concepts in mind.

The Kucherlapati patent discloses the use of YACs to express human Ig genes in a transgenic mouse environment. Examples I-IV concern inactivation of endogenous mouse Ig genes. Examples V, VI and VII concern the cloning and introduction of human Ig heavy and κ chains into mice. Example VIII concerns the cross-breeding to

obtain transgenic mice and Example IX concerns the production of monoclonal antibodies in germline chimeric mice.

Kucherlapati, however, makes no enabling disclosure of transgenic mice that have polynucleotides encoding human λ light chain, such as the Vλ genes of cluster A and all the human Jλ- Cλ segments in an authentic configuration. In fact, prior to the present invention, the only human light genes have been integrated into transgenic mice are the κ genes. *See* applicants' specification at page 3, lines 10-13. Kucherlapati's bare mention of the λ chains in column 11, line 33 is, at most, an invitation to experiment. However, the question of patentability does not revolve upon whether the prior art instills the skilled person with some type of desire to undertake inventive efforts, but rather whether the prior art suggests the claimed subject matter itself to the person of ordinary skill in the art. *See Gillette Co. v. S.C. Johnson & Son*, 10 USPQ2d 1923, 1928 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988) (holding that a reference that invites experimentation or renders something 'obvious to try' cannot satisfy the strictures of 35 USC § 103). As explained in applicants' specification at page 3, lines 13-20, prior to the present invention human antibodies containing λ sequences had not been expressed in transgenic mice, and Kucherlapati does not change that fact.

Turning to the secondary references, Mendez discloses the constructions of YACs that contain "large contiguous fragments of the human heavy and kappa (κ) light chain immunoglobulin (Ig) in nearly germline configuration...." See the Mendez abstract on page 146. Thus, Mendez's teachings are the same as Kucherlapati's in that

both concern the human heavy and κ chains, but not the human λ chain. Thus, Mendez does not modify Kucherlapati in any sense that is meaningful to the present invention.

Turning to Popov, although it discloses a Hulgλ YAC containing a 380 kb region of the human λ light chain locus, it provides no concrete example of a transgenic mouse containing such a YAC. Furthermore, neither Popov nor Kucherlapati nor Mendez suggest or disclose that a mouse comprising as a translocus a YAC containing at least a majority of the human Vλ genes of cluster A and all of the human Jλ- Cλ segments in germline configuration would show high and efficient expression of the translocus and that the translocus would be able to compete equally with the endogenous mouse κ locus.

On the latter point, it is known that mice normally produce κ and λ light chains in very different proportions. While 95% of the immunoglobulins in mice carry κ light chains, only 5 % of the antibodies carry λ light chains (see application, page 1, lines 8-9). This low presence of λ light chains is associated with markedly diminished diversity in mice. In contrast to the κ system with multiple V region families, λ light chains in mice will mainly use only one V region (λ1). The present inventors were the first to demonstrate that the introduction of at least a majority of the human Vλ genes of cluster A and all of the human Jλ- Cλ segments into mice completely alters the normal mouse pattern of expression of light chains to the situation that is closer to that found in humans (60 % κ and 40 % λ light chains). This fact is an unexpected finding since it indicates that the human translocus is driving the level of expression of the light chain genes. Moreover, the translocus is changing the pattern of the immunoglobulin

repertoire to one resembling the pattern seen in humans. Thus, more antibodies in the transgenic mice of the present invention carry λ light chains, and even the endogenous λ light chain genes are inhibited. This very important finding was impossible to predict from the design of the transgene alone. This finding makes the transgenic mice attainable according to the invention very useful for generating human antibodies.

Similarly, as noted by the examiner, Mendez mentions that in "xenomouse I" mice containing "one allele of smaller Ig YACs", an "equal distribution of human κ and mouse λ" was detected (page 148, column 2 and page 153, column 1). In contrast to the smaller human Ig YACs used in xenomouse I, Mendez's work suggests that when larger human Ig YACs are transfected into mice (to form xenomouse II in Mendez), mouse-like regulation would be observed. Thus, for xenomouse II, the light chain distribution ratio approaches "that observed in wild-type mice, indicating a mouse-like regulation of light chain utilization" (Mendez page 148, column 2). Therefore, contrary to the assertions of the examiner, the finding in the present application is unexpected in the light of Mendez.

The present invention shows high and efficient expression of the translocus in the transgenic mouse. In both Mendez and Kucherlapati, endogenous mouse heavy and κ genes were deleted in the test mice to show expression of transfected human immunoglobulin genes. However, in the transgenic mouse of the present invention, human λ genes could be efficiently expressed even in the presence of the endogenous mouse counterparts, which is the opposite of what was thought to be true according to the art. See application at page 12, lines 20-22. This finding allows for the production of antibodies comprising high levels of human λ light chains in commercial mice

regardless of whether these mice are silenced for endogenous immunoglobulin gene expression, and is considered to be surprising by the skilled person.

The surprising results obtained with the present invention further establish patentability, and the examiner has not demonstrated anything to the contrary. *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); MPEP § 716.02(a) (August 2001). As explained by the Federal Circuit:

> [W]hen an applicant demonstrates *substantially* improved results ... and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary.

In re Soni, 34 USPQ2d 1684, 1688 (Fed. Cir. 1995) (emphasis in original).

For at least these reasons, applicants submit that the person having ordinary skill in the art would not consider the present invention obvious over the disclosures and teachings of Kucherlapati, Mendez and Popov. Accordingly, applicants respectfully request withdrawal of the rejection.

The claims are readily understood by the skilled person, and thus are definite

For definiteness, a claim need only reasonably apprise those skilled in the art of the utilization and scope of the invention. *Hybritech, Inc. v. Monoclonal Antibodies,* 231 USPQ 81, 94-95 (1986). Words are to be given their plain meaning as understood by the person of ordinary skill in the art, particularly given the limitations of the English language. *See* MPEP §§ 707.07(g); 2111.01 (August 2001). Claims are to be given their broadest reasonable interpretation consistent with applicants' specification. *See* MPEP § 2111 (August 2001). In sum, in order to reject the claims on definiteness

grounds, it is incumbent on the examiner to show how and why the skilled person having applicants' specification would not be apprised of the invention by the language-at-issue.

With respect to claim 4, the person of skill would immediately realize that the claimed transgenic mouse would implicitly contain κ light chain genes. The κ light chains genes could, for example, be endogenous genes and/or transgenic genes. Applicants therefore request withdrawal of the rejection.

The examiner states that "the YAC in step (a) of claim 7 cannot be introduced into the murine embryonic stem cells in the absence of protoplast fusion, see the limitations of claim 10". This is statement is incorrect, however. Protoplast fusion is only one of the possible ways known to the skilled person for introducing a YAC into murine embryonic stem cells. Other known methods include DNA microinjection and lipofection. Protoplast fusion is one preferred approach (as recited in claim 10) because YAC DNA does not need to be purified and in most cases a single complete copy of the YAC is integrated. The advantages of protoplast fusion make is desirable, but not required. Applicants therefore request withdrawal of the rejection.

Request

Applicants submit that the claims are in condition for allowance, and respectfully request favorable consideration to that effect. The examiner is invited to contact the undersigned at (202) 912-2000 should there be any questions.

Respectfully submitted,

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Marked-Up Copy of Amended Claims

1. (Amended) A transgenic mouse comprising as a translocus a **yeast artificial chromosome (**YAC**)** of about 410 Kb, wherein the YAC contains **at least a majority [most]** of the human Vλ genes of cluster A and all the human Jλ- Cλ segments in germline configuration, wherein the translocus shows high expression, and is able to compete **[equally]** with the endogenous mouse κ locus.

2. (Amended) A transgenic mouse comprising as a translocus a **yeast artificial chromosome (**YAC**)** of about 410 Kb, wherein the YAC contains **at least a majority [most]** of the human Vλ genes of cluster A and all the human Jλ- Cλ segments in germline configuration, wherein the mouse has one or both endogenous Igκ alleles disrupted, and wherein the translocus shows high expression.

3. (Amended) A transgenic mouse **[carrying] comprising** a 380 Kb region of the human immunoglobulin (Ig) λ light (L) chain locus in germline configuration, wherein the **[introduced translocus] 380 Kb region** resides on a yeast artificial chromosome (YAC) that accommodates the most proximal V (variable gene) λ cluster **[- with 15 V λ genes that contribute to over 60% of λ light chains in man - and all J λ- C λ segments with the 3' region including the downstream enhancer], wherein**

the 380 Kb regions has 15 V λ genes and all J λ- C λ segments with the 3' region, wherein the 3' region includes a downstream enhancer.

4. (Amended) A transgenic mouse comprising human Ig lambda genes in which the proportion of the κ and λ light chains expressed by said **[human lambda genes] transgenic mouse** resembles that found in humans, and exhibits relative proportions of ≤60% κ light chains and ≥40% λ light chains.

7. (Amended) A method for producing a transgenic mouse according to claim 1, comprising:

(a) introducing a Hulgλ YAC into murine embryonic stems cells; and

(b) deriving a transgenic mouse from the cells of step (a) **by blastocyte injection to form a chimeric animal and then breeding the chimeric mouse to obtain a transgenic mouse**.

17. (Amended) The transgenic mouse according to claim 16, wherein the YAC includes a 380 Kb region of the human Igλ locus in authentic configuration with **at least a majority of [most]** Vλ genes of cluster A, Jλ-Cλ segments and **[the] a** 3' enhancer.

18. (Amended) A transgenic mouse comprising variable, joining and constant genes of the human λ light chain locus as a transgenic locus on a **yeast**

artificial chromosome (YAC), wherein B cells of said **[mice] mouse** rearrange said λ light chain genes and the **[mice] mouse** expresses serum immunoglobulins containing human λ light chains.

22. (Amended) The transgenic mouse carrying human λ light chain genes according to claim 21, wherein the second transgenic locus carries a diversity of human heavy chain constant region genes**[, including] and includes** μ, δ and γ genes.

23. (Amended) The transgenic mouse carrying human λ light chain genes and human heavy chain genes according to claim 22, wherein the heavy chain transgenic locus carries a diversity of human heavy chain constant region genes **[, including] and includes** μ, δ and γ genes, **wherein the heavy chain constant region genes are** in authentic germline configuration.

25. (Amended) The transgenic mouse carrying human λ light chain genes according to claim 16, further comprising human heavy chain genes as a second transgenic locus and human κ light chain genes as a third transgenic locus, wherein the mouse expresses serum immunoglobulin molecules containing human heavy chains in combination with **at least one of** human κ or λ light chains.

26. (Amended) The transgenic mouse carrying human λ light chain genes according to claim 16, wherein expression of the endogenous mouse heavy and/or light

chain loci has been prevented [through gene targeting or other means] and which expresses serum immunoglobulin containing human heavy and/or light chains**, wherein the transgenic mouse is [and which are]** deficient in production of mouse immunoglobulin.

27. (Amended) A transgenic mouse carrying human λ light chain genes in which expression of the human λ locus is equal to or greater than that of **[the endogenous or transgenic human] a** κ locus.